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<p>(21) International Application Number: PCT/JP97/04243</p> <p>(22) International Filing Date: 20 November 1997 (20.11.97)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>PO 4219</td> <td>16 December 1996 (16.12.96)</td> <td>AU</td> </tr> <tr> <td>PO 5929</td> <td>1 April 1997 (01.04.97)</td> <td>AU</td> </tr> <tr> <td>PO 9030</td> <td>9 September 1997 (09.09.97)</td> <td>AU</td> </tr> </table> <p>(71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).</p> <p>(71) Applicant (for US only): YATABE, Yoshiko (heiress of the deceased inventor) [JP/JP]; 4-1-1-421-201, Namiki, Tsukuba-shi, Ibaraki 305 (JP).</p> <p>(72) Inventor: YATABE, Takumi (deceased).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): ITOH, Yoshikuni [JP/JP]; 2-49-12, Himuro-cho, Takatsuki-shi, Osaka 569-11 (JP). INOUE, Takayuki [JP/JP]; 4-15-2-2-201, Matsushiro, Tsukuba-shi, Ibaraki 305 (JP). HAMASHIMA, Hitoshi [JP/JP]; 3-25-4-202, Matsushiro, Tsukuba-shi, Ibaraki</p>	PO 4219	16 December 1996 (16.12.96)	AU	PO 5929	1 April 1997 (01.04.97)	AU	PO 9030	9 September 1997 (09.09.97)	AU	<p>305 (JP). SHIMA, Ichiro [JP/JP]; 5-25-105, Gosyogaoka, Moriya-cho, Kitasouma-gun, Ibaraki 302-01 (JP). OHNE, Kazuhiko [JP/JP]; 1-16-15-A102, Ninomiya, Tsukuba-shi, Ibaraki 305 (JP). YOSHIHARA, Kousei [JP/JP]; 2-4-38-405, Manabe, Tsuchiura-shi, Ibaraki 300 (JP). OKU, Teruo [JP/JP]; 8-2, Midorigaoka, Tsukuba-shi, Ibaraki 305 (JP).</p> <p>(74) Agent: TAKASHIMA, Hajime; Yuki Building, 3-9, Hiranomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).</p> <p>(81) Designated States: AU, CA, CN, HU, IL, JP, KR, MX, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published Without international search report and to be republished upon receipt of that report.</p>
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(54) Title: NEW AMIDE COMPOUNDS

(57) Abstract

A compound of formula (I) wherein each symbol is as defined in the specification, and pharmaceutically acceptable salts thereof. The compound (I) of the present invention and pharmaceutically acceptable salts thereof possess a strong inhibitory activity on the production of nitric oxide (NO), and are useful for prevention and/or treatment of NO-mediated diseases such as adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, synovitis, shock, diabetes, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, glomerulonephritis, peptic ulcer, inflammatory bowel disease, cerebral infarction, cerebral ischemia, cerebral hemorrhage, migraine, rheumatoid arthritis, gout, neuritis, postherpetic neuralgia, osteoarthritis, osteoporosis, systemic lupus erythematosus, rejection by organ transplantation, asthma, metastasis, Alzheimer's disease, arthritis, CNS disorders, dermatitis, hepatitis, liver cirrhosis, multiple sclerosis, pancreatitis, atherosclerosis, and the like in human being and animals.

$$R^1-\text{CON}-R^2-(Y)-\text{N}=\text{C}(\text{R}^5)-\text{C}(\text{R}^4)=\text{C}(\text{X})-\text{N} \quad (I)$$

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DESCRIPTION
NEW AMIDE COMPOUNDS

TECHNICAL FIELD

This invention relates to new amide compounds and pharmaceutically acceptable salts thereof which are useful as medicament.

BACKGROUND ART

Some peptide compounds have been known as described, for example, in EP 0 394 989 A2.

DISCLOSURE OF INVENTION

This invention relates to new amide compounds.

One object of this invention is to provide the new and useful amide compounds and pharmaceutically acceptable salts thereof which possess a strong inhibitory activity on the production of nitric oxide (NO).

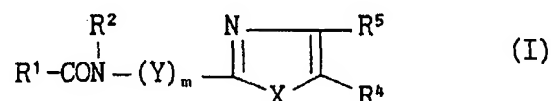
Another object of this invention is to provide a process for the preparation of the amide compounds and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising said amide compound or a pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a use of said amide compounds or pharmaceutically acceptable salts thereof as a medicament for prophylactic and therapeutic treatment of NO-mediated diseases such as adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, synovitis, shock (e.g., septic shock, etc.), diabetes (e.g., insulin-dependent diabetes mellitus, etc.), diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, glomerulonephritis, peptic ulcer, inflammatory bowel disease (e.g., ulcerative colitis, chronic colitis, etc.), cerebral

infarction, cerebral ischemia, cerebral hemorrhage, migraine, rheumatoid arthritis, gout, neuritis, postherpetic neuralgia, osteoarthritis, osteoporosis, systemic lupus erythematosus, rejection by organ transplantation, asthma, metastasis, Alzheimer's disease, arthritis, CNS disorders, dermatitis, hepatitis, liver cirrhosis, multiple sclerosis, pancreatitis, atherosclerosis, and the like in human being and animals.

The object amide compounds of the present invention are novel and can be represented by the following general formula (I)



wherein

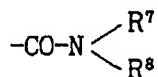
R¹ is indolyl which may have a suitable substituent selected from the group consisting of lower alkyl, phenyl, halogen, lower alkoxy, and nitro, benzofuranyl, phenyl which may have one or two suitable substituent(s) selected from the group consisting of amino, acylamino, lower alkylamino, halogen, lower alkoxy and nitro, lower alkyl, quinoxaliny, quinolyl, pyrrolyl, pyrimidinyl having benzofuranyl, benzimidazolyl, benzothienyl, benzothiazolyl, benzoxazolyl, indoliny, anilino, phenylcarbamoyl or imidazolyl which may have one or two suitable substituent(s) selected from the group consisting of phenyl, lower alkyl and indolyl;

R² is hydrogen or phenyl(lower)alkyl;

R⁴ is hydrogen, phenyl or pyridyl, each of which may have suitable substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkylthio, halogen, trihalomethyl, nitro, cyano, imidazolyl, optionally protected hydroxy, acyl, amino, acylamino, diacylamino, di(lower)alkylamino, amino(lower)alkyl, acylamino(lower)alkyl, pyrazolyl,

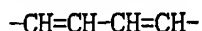
morpholinyl, piperidyl, triazolyl, lower alkoxy(lower)alkoxy, hydroxy(lower)alkyl, lower alkylpiperazinyl, phenyl and carboxy, quinolyl or 3,4-methylenedioxyphenyl;

R⁵ is hydrogen, imidazolyl, phenyl, nitrophenyl, phenyl(lower)alkyl, optionally esterified carboxy or a group of the formula



in which R⁷ and R⁸ are the same or different and each is hydrogen, phenyl, phenyl(lower)alkyl, lower alkyl or lower alkoxy; or

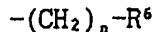
R⁴ and R⁵ in combination form a group of the formula



Y is a group of the formula

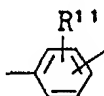


in which R³ is hydrogen or a group of the formula



in which R⁶ is optionally protected hydroxy, acyl, carboxy, acylamino, lower alkoxy, phenyl(lower)alkoxy, lower alkylthio, phenyl which may have a suitable substituent selected from the group consisting of lower alkoxy, halogen, amino, acylamino, diacylamino and nitro, pyridyl which may have a suitable substituent selected from the group consisting of lower alkoxy and halogen, pyrazinyl, pyrimidinyl, furyl, imidazolyl, naphthyl, N-(lower)-alkylindolyl or 3,4-methylenedioxyphenyl, and n is an integer of 0 to 3,

or a group of the formula



in which R¹¹ is phenyl, phenoxy or phenyl(lower)alkoxy; or

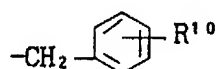
R² and R³ in combination form a group of the formula



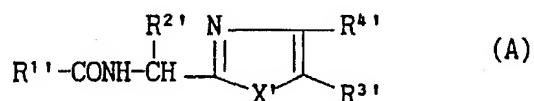
m is 0 or 1; and

X is S or NR⁹

in which R⁹ is hydrogen, lower alkyl, cyclo(lower)alkyl or a group of the formula



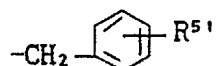
in which R¹⁰ is hydrogen, lower alkyl or lower alkoxy;
or a pharmaceutically acceptable salt thereof,
provided that the compound shown below is excluded:
a compound of the formula



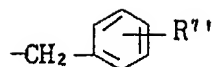
wherein

R^{1'} is indolyl or benzofuranyl;

R^{2'} is hydrogen, lower alkylthio(lower)alkyl or a group of the formula



in which R^{5'} is hydrogen, lower alkoxy or halogen;
R^{3'} is hydrogen, quinolyl or phenyl which may have a suitable
substituent selected from the group consisting of lower alkyl,
lower alkoxy, lower alkylthio and halogen;
R^{4'} is hydrogen or optionally esterified carboxy; and
X' is S or NR^{6'}
in which R^{6'} is hydrogen, lower alkyl or a group of the formula



in which R'' is lower alkyl or lower alkoxy,
and a pharmaceutically acceptable salt thereof.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and include, for example, a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, citrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); and a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "lower alkylthio", "lower alkylthio(lower)alkyl", "N-(lower)-alkylindolyl", "lower alkylamino", "di(lower)alkylamino",

"phenyl(lower)alkyl", "amino(lower)alkyl", "acylamino(lower)alkyl", "hydroxy(lower)alkyl" and "lower alkylpiperazinyl" include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl, in which more preferred one is C₁-C₄ alkyl.

Suitable "lower alkoxy" and "lower alkoxy moiety" in the terms "lower alkoxy(lower)alkoxy" and "phenyl(lower)alkoxy" include, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy and hexyloxy, in which more preferred one is C₁-C₄ alkoxy.

Suitable "halogen" includes, for example, fluorine, bromine, chlorine and iodine.

"Optionally esterified carboxy" includes carboxy and esterified carboxy. Suitable examples of said ester include lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, tert-pentyl ester, hexyl ester, etc.); lower alkenyl ester (e.g., vinyl ester, allyl ester, etc.); lower alkynyl ester (e.g., ethynyl ester, propynyl ester, etc.); lower alkoxy(lower)alkyl ester (e.g., methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.); mono(or di or tri)-aryl(lower)alkyl ester, for example, mono(or di or tri)phenyl(lower)-alkyl ester which may have one or more suitable substituent(s) [e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.]; and aryl ester which may have one or more suitable substituent(s) such as substituted or unsubstituted phenyl ester (e.g., phenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, 4-chlorophenyl ester, 4-methoxyphenyl ester, etc.).

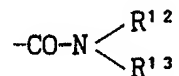
Suitable "trihalomethyl" includes, for example, trifluoromethyl,

trichloromethyl and tribromomethyl, in which preferred one is trifluoromethyl.

Suitable "amino protective group" includes, for example, acyl and conventional protective group such as mono(or di or tri)aryl(lower)-alkyl, for example, mono(or di or tri)phenyl(lower)alkyl (e.g., benzyl, trityl, etc.).

Suitable "acyl" and "acyl moiety" in the terms "acylamino", "diacylamino" and "acylamino(lower)alkyl" include, for example, carbamoyl which may be substituted by suitable substituent(s), aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or a heterocyclic ring, which is referred to as heterocyclic acyl.

Suitable examples of said acyl are illustrated as follows:
 "carbamoyl which may be substituted by suitable substituent(s)" includes a group of the formula



wherein R^{12} and R^{13} are the same or different and each is hydrogen, lower alkyl, phenyl which may have a suitable substituent selected from the group consisting of lower alkoxy and halogen, phenyl(lower)-alkyl, pyridyl, pyridyl(lower)alkyl or 3,4-methylenedioxyphenyl; aliphatic acyl such as lower alkanoyl which may be substituted by one to three halogen atoms (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, trichloroacetyl, trifluoroacetyl, etc.), lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, tert-pentyloxycarbonyl, etc.), lower alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.), lower alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.), cyclo(lower)alkylcarbonyl (e.g., cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), and the like; aromatic acyl such as aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.), aryl(lower)alkanoyl [e.g., phenyl(lower)alkanoyl (e.g., phenylacetyl,

phenylpropanoyl, phenylbutanoyl, etc.), naphthyl(lower)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.], aryl(lower)alkoxycarbonyl [e.g., phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), etc.], aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.), aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.), arylsulfonyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.), and the like; heterocyclic acyl such as indolylcarbonyl (e.g., indolyl-2-ylcarbonyl, etc.), benzofuranylcarbonyl (e.g., benzofuran-2-ylcarbonyl), quinoxalinylcarbonyl, quinolylcarbonyl, pyrrolylcarbonyl, benzimidazolylcarbonyl, benzothienylcarbonyl, benzothiazolylcarbonyl, imidazolylcarbonyl, pyridylcarbonyl, morpholinylcarbonyl (e.g., morpholinocarbonyl) and the like.

"Optionally protected hydroxy" includes hydroxy and protected hydroxy. Suitable examples of "hydroxy protective group" in the term "protected hydroxy" include acyl (e.g., acetyl, trichloroacetyl, etc.), mono(or di or tri)phenyl(lower)alkyl which may have one or more suitable substituent(s) (e.g., benzyl, 4-methoxybenzyl, trityl, etc.), trisubstituted silyl [e.g., tri(lower)alkylsilyl (e.g., trimethylsilyl, tert-butyldimethylsilyl, etc.), etc.], tetrahydropyranyl and the like.

Suitable "protected carboxy" is carboxy group protected by conventional protective group such as lower alkoxycarbonyl [e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, sec-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, neopentyloxycarbonyl, hexyloxycarbonyl, etc.], optionally substituted phenyl(lower)-alkoxycarbonyl for example, mono- or di- or triphenyl(lower)-alkoxycarbonyl which may be substituted by nitro [e.g., benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, benzhydryloxycarbonyl, trityloxycarbonyl, etc.] and the like.

Suitable "cyclo(lower)alkyl" includes cycloalkyl having 3 to 6

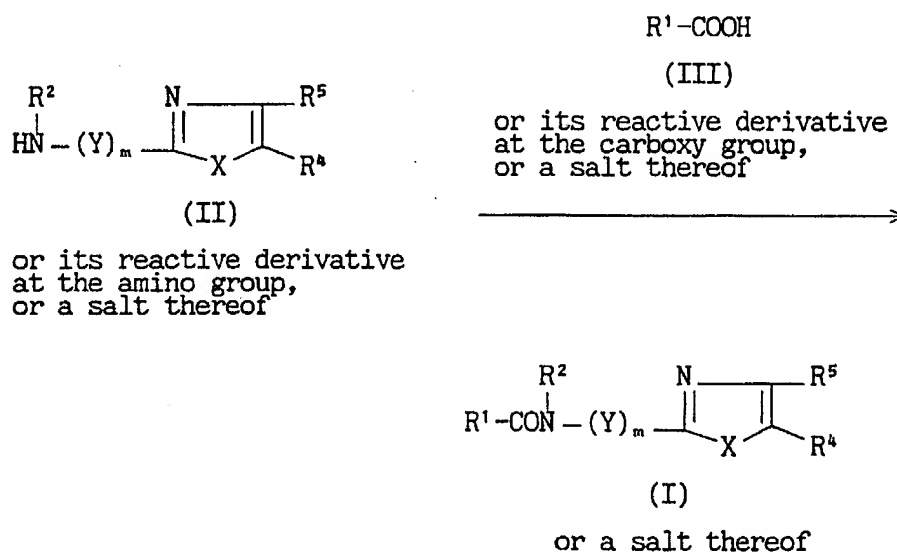
carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, in which more preferred ones are cyclopropyl and cyclobutyl.

The term "morpholinyl" includes 2-morpholinyl, 3-morpholinyl and 4-morpholinyl (i.e. morpholino).

The term "piperidyl" includes 1-piperidyl (i.e. piperidino), 2-piperidyl, 3-piperidyl and 4-piperidyl.

The object compound (I) of the present invention can be prepared by the following processes.

Process (1)



bond(s), and all of such isomers and mixtures thereof are included within the scope of this invention.

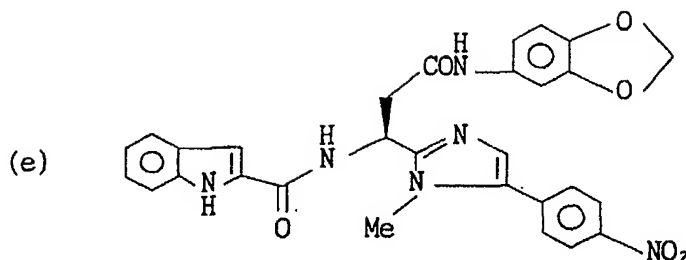
The object compounds (I) and pharmaceutically acceptable salts thereof include solvates [e.g., enclosure compounds (e.g., hydrate, etc.)].

The object compounds (I) and pharmaceutically acceptable salts thereof possess a strong inhibitory activity on the production of nitric oxide (NO).

Accordingly, the object compounds (I) and pharmaceutically acceptable salts thereof are expected to possess a nitric oxide synthase (NOS)-inhibitory activity or a NOS-production inhibitory activity.

Accordingly, they are useful for prevention and/or treatment of NO-mediated diseases such as adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, synovitis, shock (e.g., septic shock, etc.), diabetes (e.g., insulin-dependent diabetes mellitus, etc.), diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, glomerulonephritis, peptic ulcer, inflammatory bowel disease (e.g., ulcerative colitis, chronic colitis, etc.), cerebral infarction, cerebral ischemia, cerebral hemorrhage, migraine, rheumatoid arthritis, gout, neuritis, postherpetic neuralgia, osteoarthritis, osteoporosis, systemic lupus erythematosus, rejection by organ transplantation, asthma, metastasis, Alzheimer's disease, arthritis, CNS disorders, dermatitis, hepatitis, liver cirrhosis, multiple sclerosis, pancreatitis, atherosclerosis, and the like.

In order to illustrate the usefulness of the object compound (I), the pharmacological test result of the representative compound of the compound (I) is shown in the following.



Test : Assay for inhibitory activity on the production of nitric oxide

The murine macrophage cell line RAW264.7 (American Type Culture Collection, No. TIB71) was used in this study. RAW264.7 cells were grown on F75 plastic culture flasks at 37°C, 5% in Dulbecco's modified Eagle's medium (DMEM) supplemented with L-glutamine, penicillin, streptomycin and 10% heat-inactivated fetal bovine serum. They were removed from culture flasks by rubber cell scraper and were centrifuged and resuspended in DMEM without phenol red. They were plated in 96-well microtiter plates (10⁵ cells per well) and allowed to adhere over 2 hours. The test samples were added and the cells were preincubated for 1 hour. Thereafter the cells were activated with both of lipopolysaccharide (LPS) (1 μg/ml) and interferon γ (INF γ) (3 u/ml) for 18-24 hours. An equal volume of Griess reagent (1% sulfanilamide/0.1% N-naphthylethylenediamine dihydrochloride/2.5% H₃PO₄) was added and the cells were incubated at room temperature for 10 minutes. The absorbance was read at 570 nm using microplate reader and NO₂⁻ was measured using NaNO₂ as a standard.

Test result :

Test compound (10 ⁻⁵ M)	Inhibition (%)
(a)	100
(b)	100
(c)	100
(d)	100
(e)	100

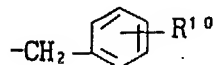
For therapeutic administration, the object compound (I) of the present invention and pharmaceutically acceptable salts thereof are used in the form of a conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration. The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee, suppository or ointment, or in a liquid form such as solution, suspension or emulsion for injection, intravenous drip, ingestion, eye drop, etc. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

The effective ingredient may usually be administered in a unit dose of 0.001 mg/kg to 500 mg/kg, preferably 0.01 mg/kg to 10 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, body weight and conditions of the patient or administering method.

The preferred embodiments of the amide compounds of the present invention represented by the general formula (I) are as follows.
R' is indolyl which may have a suitable substituent selected from the group consisting of lower alkyl, phenyl, halogen, lower alkoxy, and nitro, benzofuranyl, phenyl which may have one or two

X is NR⁹

in which R⁹ is hydrogen, lower alkyl, cyclo(lower)alkyl or a group of the formula



in which R¹⁰ is hydrogen, lower alkyl or lower alkoxy;
or a pharmaceutically acceptable salt thereof.

The following Preparations and Examples are given for the purpose of illustrating the present invention in detail.

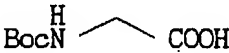
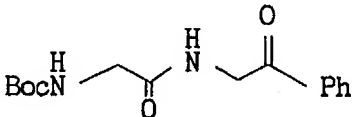
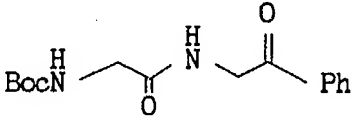
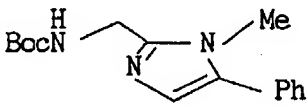
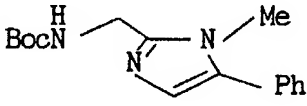
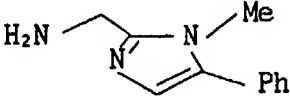
In the following Examples and Preparations, there are employed the other abbreviations in addition to the abbreviations adopted by the IUPAC-IUB (Commission on Biological Nomenclature).

The abbreviations used are as follows.

Boc : tert-butoxycarbonyl
Me : methyl
Et : ethyl
Pr : propyl
i-Pr : isopropyl
Bu : butyl
Ph : phenyl
Ts : p-toluenesulfonyl
Ac : acetyl
Bn : benzyl
Cbz : benzlyoxycarbonyl
Tf : trifluoromethanesulfonyl

The starting compounds used and the object compounds obtained in the following Preparations and Examples are given in the Tables as below, in which the formulae of the starting compounds are in the upper and the formulae of the object compounds are in the lower, respectively.

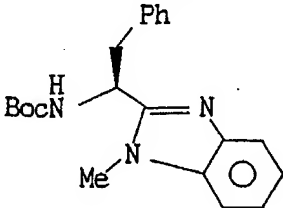
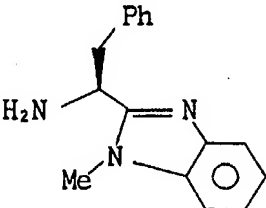

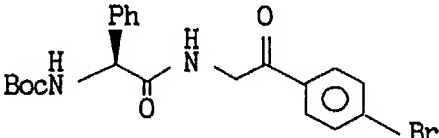
Table

Preparation No.	Formula
1	
	
2	
	
3	
	

Table

Preparation No.	Formula
60	
61	
62	

Table

Preparation No.	Formula
63	
	
64	
	
65	